to oligonucleotide phosphotriesters (Figure 1e).

The borane (BH_3) group is isoelectronic with oxygen and the boranophosphate internucleotide group is negatively charged like the normal O-oligonucleotides. The borane group is also isoelectronic, as well as isostructural, with the oligonucleotide methylphosphonates, which are nuclease resistant. Thus, the boranophosphate linkage may permit the construction of an important and perhaps ideal antisense species in that the nucleotide bases are unaltered (and thus should maintain binding specificity) while the backbone remains negatively charged (and thus should be water soluble) like the O-oligonucleotide. Since BH_3 is much more hydrophobic than oxygen, it may impart a greater membrane permeability than the O-oligonucleotide yet maintain nuclease resistance like the methylphosphonates. Although compounds containing boron–hydride bonds are susceptible to hydrolysis, the B–H bond in boranophosphates possesses unusual hydrolytic stability, as shown below.

The boronated oligonucleotides were prepared according to the method described in Scheme I. Reaction of 5′-DMT-thymidine phosphoramidite with 3′-acetylthymidine in the presence of tetrazole results in the formation of an intermediate phosphite,[6] which is then converted to the dithymidyl boranophosphate methyl ester, **1**, by reaction with dimethyl sulfide–borane (Scheme I). Both reactions can be easily followed by ^{31}P NMR. In the first reaction the amidite peaks at 148.75 and 148.42 ppm were replaced by the new phosphite peaks at 140.41 and 139.80 ppm within the time required for recording the spectrum. In the second reaction the phosphite peaks disappeared within 5–10 min; after a large number of accumulations, a broad peak at 118.0 ppm for boranophosphate phosphorus was observed.

The oxidation step with $Me_2S{\cdot}BH_3$ confers another advantage. In addition to the formation of the desired boranophosphate linkage, it also removes the DMT protecting group from the 5′-hydroxyl position and hence eliminates the extra 5′-deprotection step that is required for chain elongation.

Dimer **1** was purified by flash chromatography followed by reverse-phase HPLC to give an overall yield of 52%. It has been extensively characterized by ^1H NMR (including COSY and HOHAHA techniques), ^{11}B NMR, ^{13}C NMR, ^{31}P NMR, and fast atom bombardment (FAB) mass spectroscopies. Satisfactory elemental analyses for C, H, N, and P (within ±0.4%) have been obtained.

Dimer **1** reacts with concentrated NH_4OH at room temperature, hydrolyzing the POMe and the 3′-acetate groups to give the unprotected dinucleoside boranophosphate **2** (Scheme I), without any detectable degradation of the internucleotide or the glycosidic bonds. The deprotected boronated dimer is very soluble in water as compared to its protected counterpart, which is sparingly soluble. This product has also been characterized by ^1H NMR (including COSY), ^{11}B NMR, ^{31}P NMR, and FAB mass spectroscopies. In the ^1H NMR of **2**, two sets of peaks (for two diastereomers) were observed as opposed to only a single set of peaks (for both diastereomers) observed in the case of **1**.

The internucleotide boranophosphate group is very stable toward basic or acidic hydrolysis. Thus, heating **1** at 55 °C overnight in concentrated NH_4OH (conditions used for deprotection of bases in normal oligonucleotide synthesis) does not result in any change other than the deprotection described above. The boranophosphate group is also remarkably stable under acidic conditions. When shaken at room temperature overnight in a mixture of 1 N HCl and MeOH (1:1 v/v), <10% of the boranophosphate group is converted into phosphate (by ^{11}B and ^{31}P NMR). The 3′-acetate group is hydrolyzed although the POMe group appears to remain intact (by ^1H NMR).

Further, in preliminary studies, the boranophosphate group is also stable under the conditions required for chain elongation. Thus, reaction of **1** with 5′-DMT-thymidine phosphoramidite, followed by $Me_2S{\cdot}BH_3$ results in the formation of trimer **3** (Scheme I), in which both internucleotide linkages are boranophosphate groups.[7]

Finally, the boranophosphate internucleotide linkage in dimer **2** is quite stable toward cleavage by both calf spleen phosphodiesterase and snake venom phosphodiesterase. Thus, under the conditions where normal dithymidylyl phosphate is >97% cleaved, dimer **2** is >92% stable.

In summary, we have prepared two totally new types of modified oligonucleotides in which one of the oxygens in each internucleotide linkage has been replaced with a BH_3 group. The internucleotide linkages in boranophosphates are remarkably stable toward hydrolysis under basic[8] or acidic conditions or by exonucleases. Therefore, these linkages should be stable in vivo.

Thus, these nucleotides with boronated phosphates may represent a new class of potential therapeutic agents. Since these nucleic acids contain boron, the possibility of additional therapy using the unique neutron capturing ability of the nonradioactive ^{10}B isotope[9] (to produce in situ cell killing radiation) also exists.

Acknowledgment. This work was supported by grants from the North Carolina Biotechnology Center (to Boron Biologicals, Inc.) and the National Institutes of Health (Grant RO1 CA44709 to B.R.S. and 1 R43 GM41510-01 to Boron Biologicals, Inc.). We thank Jon M. Madison for carrying out nuclease resistance studies.

(6) Beaucage, S. L.; Caruthers, M. H. *Tetrahedron Lett.* **1981**, *22*, 1859.

(7) This reaction has been carried out only once and the yield of **3** was only 5.2% (prior to HPLC, 22.4%). A large portion (ca. 66%) of dimer **1** was recovered unreacted. Clearly, the procedure must be optimized to obtain ~99% coupling before it could be used for practical synthesis of oligonucleotides.

(8) The boranophosphate methyl esters on the other hand are base sensitive. Although they are expected to be stable in vivo, a modified method, like the one used by Miller et al.[4a] for the synthesis of phosphotriester, will be required for their synthesis in solid phase.

(9) Fairchild, R. G., Brownell, G. L., Eds. *Proceedings of the First International Symposium on Neutron Capture Therapy*, Brookhaven National Laboratory, Upton, NY, October 12–14, 1983.

Stereocontrolled Total Synthesis of (−)-Anisatin: A Neurotoxic Sesquiterpenoid Possessing a Novel Spiro β-Lactone

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Anisatin (**1**) and neoanisatin (**2**), two convulsant principles isolated from the seeds of Japanese star anise (*Illicium anisatum* L.; shikimi in Japanese), are unique, highly oxygenated sesquiterpenoids characterized by a spiro β-lactone.[1,2] The structures of anisatin (**1**) and neoanisatin (**2**), except for the absolute stereochemistry, were based on both chemical and spectral studies.[2] Anisatin (**1**) and neoanisatin (**2**) are the most powerful poisons of plant origin. Recent neurochemical studies have shown **1** to be a picrotoxin-like, noncompetitive GABA antagonist.[3] Several synthetic studies focusing on these challenging molecules have been reported recently.[4] Herein we report the first total synthesis of the natural enantiomer of anisatin (**1**) via a highly stereocontrolled route. We note in advance that the present synthesis of (−)-**1** was achieved starting with bicyclic enone **4**[5] prepared from (*R*)-(+)-pulegone (**3**), and the absolute stereostructure of natural

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(2) Yamada, K.; Takada, S.; Nakamura, S.; Hirata, Y. *Tetrahedron* **1968**, *24*, 199.

(3) Kudo, Y.; Oka, J.; Yamada, K. *Neurosci. Lett.* **1981**, *25*, 83.

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(5) Vettel, P. R.; Coates, R. M. *J. Org. Chem.* **1980**, *45*, 5430.

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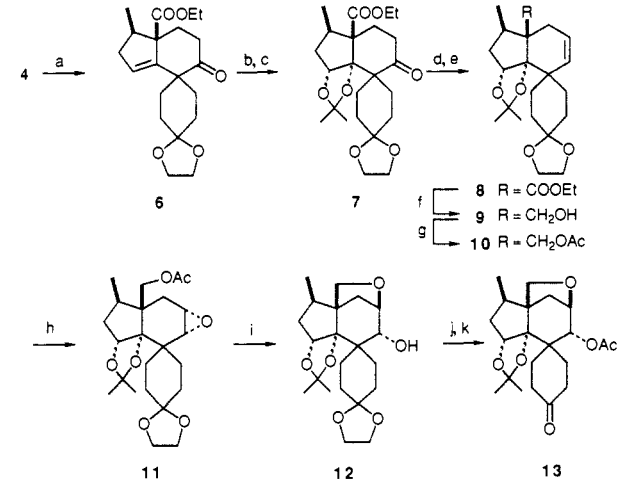
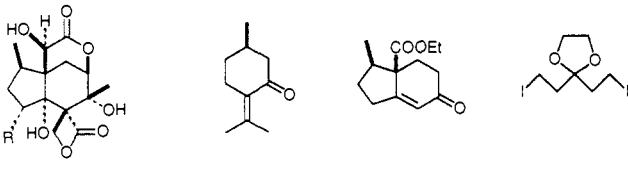
Scheme I[a]



[a] (a) NaH (3 equiv), DME, reflux, 3 h, then **5** (1.5 equiv), 60 °C, 2 h; (b) OsO_4 (1 equiv), THF–Py (1:2), 23 °C, 1.5 h; (c) $CH_2{=}C(OCH_3)CH_3$ (2.5 equiv), CSA, benzene, 23 °C, 1.5 h; (d) DIBAL (1.3 equiv), toluene, −78 °C, 1.5 h; (e) $POCl_3$ (2 equiv), Py, 90 °C, 1 h; (f) $LiAlH_4$ (20 equiv), DME, reflux, 8 h; (g) Ac_2O, DMAP, Py, 23 °C, 12 h; (h) *m*-CPBA (2.5 equiv), CH_2Cl_2, 23 °C, 10 h; (i) K_2CO_3, MeOH, 40 °C, 14 h; (j) AcOH–H_2O (4:1), 40 °C, 1 h; (k) Ac_2O, DMAP, Py, 23 °C, 18 h.

anisatin has now been established unambiguously to be as depicted in formula **1**.

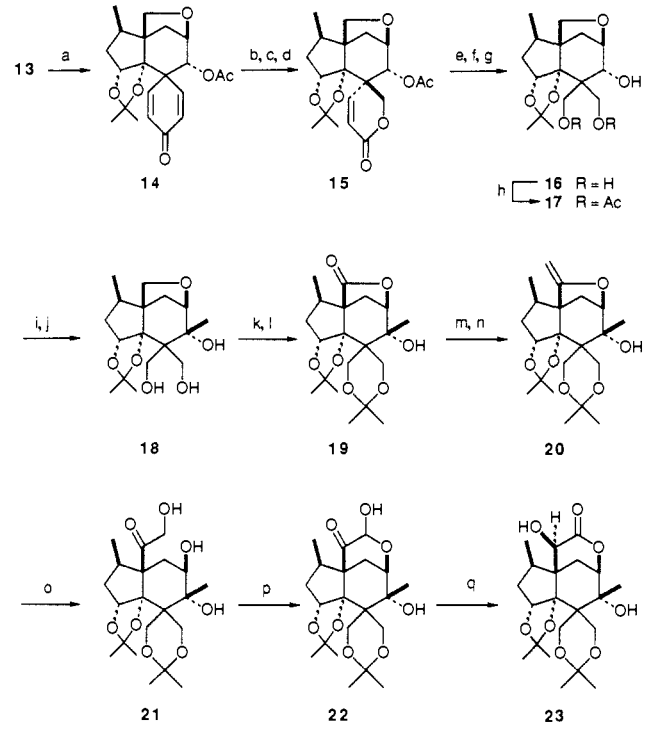


1 anisatin (R = OH) 3 4 5
2 neoanisatin (R = H)

The initial phase of the synthesis entailed introduction of a synthetic equivalent of the spiro β-lactone moiety onto **4** followed by functionalization of the *trans*-hydrindan skeleton in a stereocontrolled manner. Thus, the dienolate generated from **4** (3 equiv of NaH, DME, reflux) was reacted with diiodide **5**[6] (1.5 equiv) at 60 °C to provide spiro enone **6**[7] (83%) (Scheme I). Stereoselective cis-hydroxylation and protection as the acetonide then gave **7** (81% overall), possessing the desired trans-fused hydrindan skeleton.[8] Selective reduction of the keto group followed by dehydration of the resulting alcohol provided olefin **8** (mp 106–107 °C, 82% overall), which was transformed into acetate **10** (84% overall) via a two-step sequence: (1) reduction of **8** leading to alcohol **9** (mp 106–107 °C); (2) acetylation of **9**. Epoxidation of **10** with *m*-CPBA then proceeded stereoselectively to furnish the desired α-epoxide **11**[8,9a] (91%) as the major product. Treatment of the latter with K_2CO_3 in MeOH directly afforded cyclic ether **12** (92%) as the sole product. Removal of the ketal and acetylation furnished ketone **13** (mp 172–173 °C, 91% overall).

The next phase of the synthesis involved manipulation of the cyclohexanone ring in **13** to generate the geminal bis(hydroxymethyl) groups suitable for the construction of the spiro β-lactone. Toward this end, **13** was converted into cross-conjugated dienone

Scheme II[a]



[a] (a) $(PhSe)_2$ (0.3 equiv), *m*-iodylbenzoic acid (6 equiv), Py (4 equiv), toluene, reflux, 10 h; (b) OsO_4 (1 equiv), THF–Py (1:2), 23 °C, 1 h; (c) $Pb(OAc)_4$ (2.5 equiv), benzene–MeOH (1:1), 23 °C, 15 min; (d) $LiAlH(O\text{-}t\text{-}Bu)_3$ (4 equiv), THF, 0 °C, 2.5 h; (e) OsO_4 (1 equiv), THF–Py (1:2), 23 °C, 1 h; (f) $Pb(OAc)_4$ (1 equiv), benzene, 23 °C, 40 min; (g) $LiAlH_4$ (8 equiv), THF, 23 °C, 3 h; (h) Ac_2O, Py, 0 °C, 3 h; (i) PCC (2 equiv), CH_2Cl_2, 23 °C, 11 h; (j) CH_3MgI (100 equiv), ether, 23 °C, 1 h; (k) $CH_2{=}C(OCH_3)CH_3$ (1.3 equiv), CSA, benzene, 23 °C, 50 min; (l) $RuCl_3$ (0.01 equiv), $NaIO_4$ (5 equiv), CCl_4–CH_3CN–pH 7 phosphate buffer (1:1:2), 35 °C, 19 h; (m) CH_3Li (4 equiv), THF, 23 °C, 1 h; (n) CSA (0.1 equiv), 4-Å molecular sieves, $CHCl_3$, 23 °C, 10 min; (o) OsO_4 (3 equiv), THF–Py (1:2), 23 °C, 20 h; (p) SO_3·Py (3 quiv), DMSO (9 equiv), Et_3N (10 equiv), CH_2Cl_2, 23 °C, 1 h; (q) silica gel (for column chromatography), 23 °C, 11 h.

14 (85%) by the Barton method[10] with a slight procedural modification [i.e., $(PhSe)_2$, *m*-iodylbenzoic acid, pyridine, toluene, reflux] (Scheme II). Dienone **14** was next transformed into α,β-unsaturated lactone **15** (51% overall)[11] via a three-step sequence: (1) hydroxylation of one of the two double bonds in **14** with OsO_4; (2) oxidative cleavage of the resulting diol with $Pb(OAc)_4$; (3) reduction of the resulting aldehyde with $LiAlH(O\text{-}t\text{-}Bu)_3$.[12] The remaining double bond in **15** was cleaved in similar fashion [(1) hydroxylation with OsO_4; (2) oxidation with $Pb(OAc)_4$] to give an aldehyde, which without purification was further reduced with $LiAlH_4$ to afford triol **16**. Selective acetylation of the primary OH groups provided diacetate **17** (71% from **15**),[9b] which in turn was oxidized with pyridinium chlorochromate (PCC). The resulting ketone (mp 160–160.5 °C) was then reacted with a large excess of CH_3MgI to furnish triol **18**[8,9c] (mp 81–82 °C, 81% overall), possessing the geminal bis(hydroxymethyl) functionalities suitable for the construction of the β-lactone.

The stage was now set for construction of the α-hydroxy δ-lactone moiety in anisatin. After protection of the two hydrox-

(6) Diiodide **5** (mp 53–54 °C) was prepared from the corresponding diol (Wasylishen, R. E.; Rice, K. C.; Weiss, U. *Can. J. Chem.* **1975**, *53*, 414) in two steps: (1) TsCl–Py; (2) NaI–$CaCO_3$, acetone.

(7) Satisfactory spectral (IR, ^1H NMR, mass) and analytical (microanalyses or exact mass spectra) data were obtained for all new compounds. All yields refer to materials purified by column chromatography on silica gel.

(8) The stereochemical assignment of this compound was deduced on the basis of our model studies[4d] and was confirmed by the successful synthesis of anisatin (**1**).

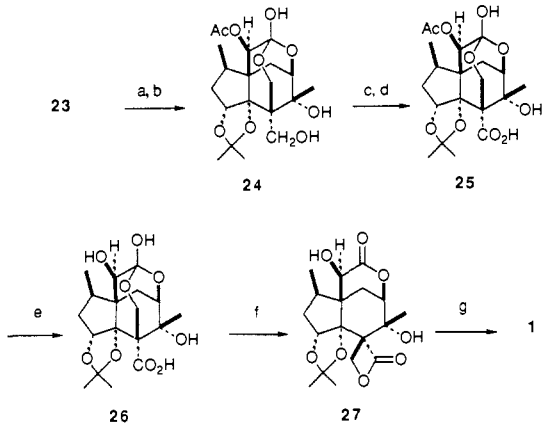
(9) A small amount of (a) the diastereomeric β-epoxide (8%); (b) the corresponding triacetate (23% from **15**); (c) the diastereomeric triol (13%) was formed.

(10) Barton, D. H. R.; Godfrey, C. R. A.; Morzycki, J. W.; Motherwell, W. B.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1947.

(11) This reaction sequence provided a single product, the stereochemistry of which was tentatively assigned as the formula **15**: we assume that the initial cis-hydroxylation of **14** may take place at the less hindered double bond, i.e., the double bond anti to the acetoxy group in **14**, leading to **15** by further transformation.

(12) Hirschmann, R.; Steinberg, N. G.; Walker, R. *J. Am. Chem. Soc.* **1962**, *84*, 1270. Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 6066.

Scheme III[a]



[a] (a) Ac_2O, DMAP, CH_2Cl_2, 23 °C, 21 h; (b) AcOH–H_2O (4:1), 35 °C, 19 h; (c) PDC (1.6 equiv), CH_2Cl_2, 23 °C, 22 h; (d) $KMnO_4$ (12.5 equiv), NaH_2PO_4 (26 equiv), *t*-BuOH–H_2O, 23 °C, 20 min; (e) K_2CO_3, MeOH, 23 °C, 4 h; (f) $PhSO_2Cl$ (6 equiv), Py–toluene (1:1), 23 °C, 9 h; (g) 2 M HCl, DME, 80 °C, 2 h.

ymethyl groups in **18** as an acetonide, the oxymethylene group was oxidized with $RuCl_3$–$NaIO_4$[13] to give γ-lactone **19** (87% overall). Reaction of **19** with CH_3Li and subsequent acidic treatment of the resulting methyl ketone provided enol ether **20** (98% overall), which upon oxidation with OsO_4 afforded α-hydroxy ketone **21** (95%). Further oxidation of **21** with SO_3·Py–DMSO–Et_3N yielded keto hemiacetal **22** (96%) as a single diastereomer.[14] The latter can be regarded as a tautomer of the desired α-hydroxy δ-lactone **23**. Isomerization of **22** into **23** was achieved smoothly by adsorbing **22** on silica gel (Fuji-Davison silica gel BW-820 MH, 80–200 mesh; $CHCl_3$ was used for adsorption and was removed by a rotary evaporator) and leaving the dried silica gel at room temperature for 11 h. Elution with ethyl acetate gave **23** (mp 248–249 °C) quantitatively. The stereochemistry of the secondary OH group in **23** was confirmed by an NOE between the α-hydrogen of the δ-lactone moiety and the secondary methyl group.

At this point all that remained to complete a synthesis of anisatin was construction of the spiro β-lactone moiety and removal of the protecting groups. Acetylation of **23** followed by selective hydrolysis of the six-membered acetonide afforded ortho ester **24** (mp 120–122 °C, 56% overall) (Scheme III), which in turn was oxidized by a two-step sequence [(1) pyridinium dichromate (PDC); (2) $KMnO_4$–NaH_2PO_4][15] to give carboxylic acid **25** (37% overall). Basic methanolysis then furnished acid **26** (mp 197–199 °C, 93%). Construction of the spiro β-lactone was achieved by reaction of **26** with $PhSO_2Cl$–Py[4c,16] to yield anisatin acetonide **27** (mp 201–204 °C, 91%). Finally, deprotection with aqueous acid provided (−)-anisatin (**1**) [99%, mp 220–222 °C, $[\alpha]^{25}_D$ −22.5° (*c* 0.118, MeOH); natural **1**, mp 220–223 °C, $[\alpha]^{26}_D$ −21.9° (*c* 0.159, MeOH)]. Chiroptical properties including the sign of specific rotation and spectral properties (^1H NMR, IR, MS) of synthetic **1** were identical with those of natural anisatin. The absolute stereostructure of anisatin is therefore as depicted in formula **1**.

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Supplementary Material Available: Spectral and physical data for compounds **6–15**, **17–21**, and **23–27** (6 pages). Ordering information is given on any current masthead page.

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Synthesis of the First Organodilithiosilane by Thermal Rearrangement

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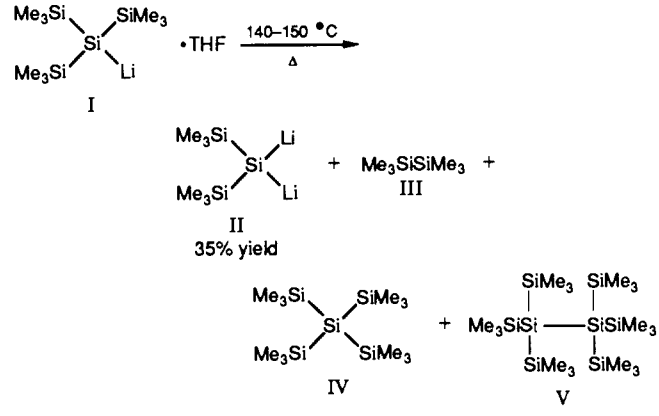
We report the synthesis of the first organodilithiosilane which we accomplished by the pyrolysis of [tris(trimethylsilyl)silyl]-lithium–THF in an inert atmosphere at 140–150 °C.



A new synthetic method has been developed in our laboratory involving pyrolysis of monolithio organic compounds which is broadly applicable in the synthesis of new substituted dilithiomethanes.[1,2] We have found that we can extend this Kawa–Lagow modified Ziegler synthetic technique[3] even beyond carbon centers to those of silicon and perhaps to other heteroatoms.

The synthesis of the first dilithiosilane, aside from having interesting possibilities for use as a chemical reagent, is of interest in view of the recent work of Streitwieser, Schleyer, and co-workers predicting the structures of both singlet and triplet dilithiosilanes.[4] Earlier, Schleyer and Reed studied the structure of tetralithiosilane and came to the conclusion that $SiLi_4$ may be the first fluxional eight-valence-electron tetracoordinate species.[5,6] Very flat potential energy surfaces and unusual geometries similar to that of the 10-electron species SF_4 are forecast for both species. It was also calculated that the potential energy surface is flat for $SiLi_4$. In 1977 our laboratory succeeded in preparing tetralithiosilane ($SiLi_4$) via lithium vapor reactions with silicon tetrachloride.[7]

The THF adduct of tris(trimethylsilyl)lithium was prepared by the reaction of tetrakis(trimethylsilyl)silane and methyllithium using a Et_2O/THF (1:4) solvent mixture.[8] The product was purified by recrystallization[9] at low temperatures. The THF adduct of compound I has excellent stability and can be stored for months at room temperature in an inert atmosphere.

$$\underset{\text{IV}}{(Me_3Si)_4Si} + MeLi \xrightarrow[4:1]{THF/Et_2O} \underset{\text{I}}{(Me_3Si)_3SiLi\cdot THF}$$

To prepare bis(trimethylsilyl)dilithiosilane, 0.6 g (184 mmol) of I was placed in a small flask coupled with a distillation apparatus. All manipulations were carried out in an oxygen-free

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